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(54) **9a-N-(N'-Carbamoyl) and 9a-N-(N'-Thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A**

9a-N-(N'-Carbamoyl)-und 9a-N-(N'Thiocarbamoyl)-Derivate von 9-Deoxo-9a-aza-9a-homoerythromycin A

Dérivés de 9a-N-(N'-carbamoyl) et de 9a-N-(N'-thiocarbamoyl) de 9-déoxo-9a-aza-9a-homoérythromycin A

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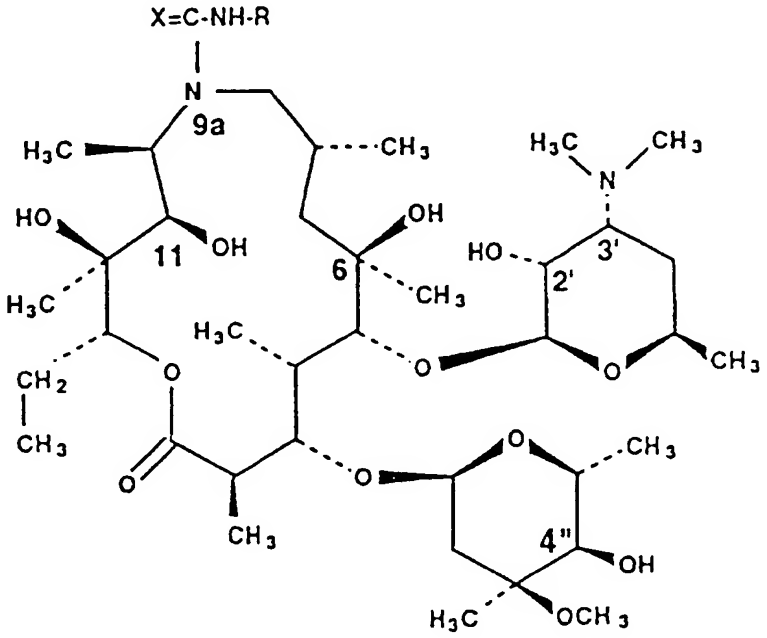
Description

The present invention relates to 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A, novel semisynthetic macrolide antibiotics of the azalide series having an antibacterial action of the general formula (I)



wherein R represents a C_1-C_3 alkyl, aryl or aralkyl group and X represents O or S, to pharmaceutically acceptable addition salts thereof with inorganic or organic acids, to a process for the preparation thereof, to a process for the preparation of the pharmaceutical compositions as well as to the use of pharmaceutical compositions obtained in the treatment of bacterial infections.

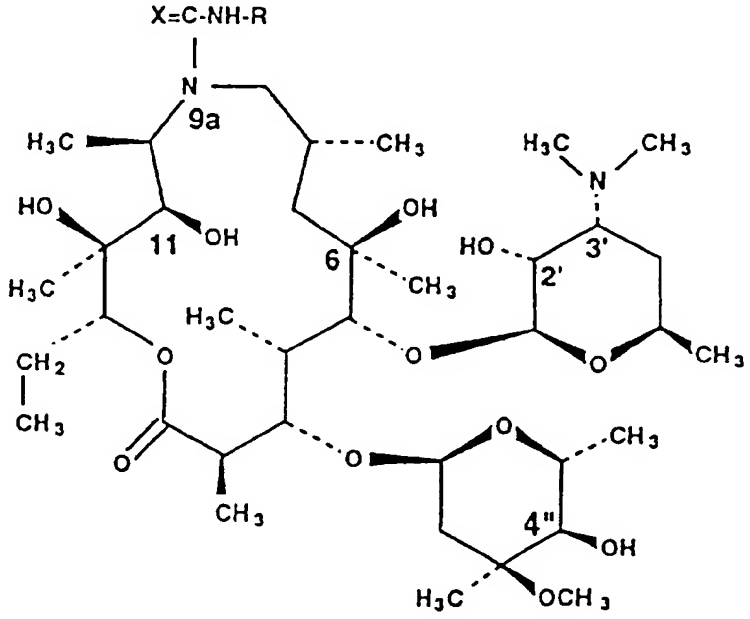
Erythromycin A is a macrolide antibiotic, whose structure is characterized by a 14-member macrolactone ring having a carbonyl group in C-9 position. It was found by McGuire in 1952 (Antibiot. Chemother., 1952; 2:281) and for over 40 years it has been considered as a reliable and effective antimicrobial agent in the treatment of diseases caused by Gram-positive and some Gram-negative microorganisms. However, in an acidic medium it is easily converted into anhydroerythromycin A, an inactive C-6/C-12 metabolite of a spiroketal structure (Kurath P. et al., Experientia 1971; 27:362). It is well-known that spirocyclisation of aglycone ring of erythromycin A is successfully inhibited by a chemical transformation of C-9 ketones or hydroxy groups in a C-6 and/or C-12 position. By the oximation of C-9 ketones (Djokié S. et al., Tetrahedron Lett, 1967; 1945) and by subsequently modifying the obtained 9(E)-oxime into 9-[O-(2-methoxyethoxy)-methyloxime] erythromycin A (OXITHROMYCIN) (Ambrieres, G. S., FR 2,473,525/1981) or 9(S)-erythromycylamine (Egan R. S. et al., J. Org. Chem., 1974; 39:2492) or a more complex oxazine derivative thereof, 9-deoxo-11-deoxy-9,11-{imino[2-(2-methoxyethxyethylidene]oxy}-9(S)-erythromycin A (DIRITHROMYCIN) (Lugar P. et al., J. Crist. Mol. Struct., 1979; 9:329), novel semisynthetic macrolides were synthetized, whose basic characteristic, in addition to a greater stability in an acidic medium, is a better pharmacokinetics and a long half-time with regard to the parent antibiotic erythromycin A. In a third way for modifying C-9 ketones use is made of Beckmann rearrangement of 9(E)-oxime and of a reduction of the obtained imino ether (Kobrehel G. et al., U.S. Pat. 4,328,334, 5/1982) into 11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo9a-aza-9a-homoerythromycin A) under broadening the 14-member ketolactone ring into a 15-member azalactone ring. By reductive N-methylation of 9a-amino group according to Eschweiler-Clarke process (Kobrehel G. et al., BE Pat. 892,357, 7/1982) or by a preliminary protection of amino group by means of conversion into the corresponding N-oxides and then by alkylation and reduction (Bright G. M., U.S. Pat. 4,474,768, 10/1984) N-methyl-11-aza-10-deoxo-10-dihydroerythromycin A (9-deoxo9a-methyl-9a-aza-9a-homoerythromycin A, AZITHROMYCIN) was synthetised, a prototype of azalide antibiotics, which, in addition to a broad antimicrobial spectrum including Gram-negative bacteria and intracellular microorganisms, are characterized by a specific

mechanism of transport to the application site, a long biological half-time and a short therapy period. In EP A 0 316 128 (Bright G. M.) novel 9a-allyl and 9a-propargyl derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A are disclosed and in U.S. Pat. 4,492,688, 1/1985 (Bright G. M.) the synthesis and the antibacterial activity of the corresponding cyclic ethers are disclosed. In the Croatian patent application 381-03/93-05/041 (559-93-1) there are further disclosed the synthesis and the activity spectrum of novel 9-deoxo-9a-aza-11-deoxy-9a-homoerythromycin A 9a,11-cyclic carbamates and O-methyl derivatives thereof.

According to the known and established Prior Art, 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A and pharmaceutically acceptable addition salts thereof with inorganic or organic acids, a process for the preparation thereof as well as the preparation methods and use an pharmaceutical preparations have not been disclosed as yet.

It has been found and it is an object of the present invention that 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A, novel semisynthetic macrolide antibiotics of the azalide series and pharmaceutically acceptable addition salts thereof with inorganic or organic acids may be prepared by reacting 9-deoxo-9a-aza-9a-homoerythromycin A with isocyanates or isothiocyanates and optionally by reacting the obtained 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A with inorganic and organic acids.

It has been found that novel 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A of the formula (I)



wherein R represents a C_1-C_3 alkyl, aryl or aralkyl group and X represents O or S, and pharmaceutically acceptable addition salts thereof with inorganic or organic acids may be prepared by reacting 9-deoxo-9a-aza-9a-homoerythromycin A with isocyanates or isothiocyanates of the general formula (II)

$$R - N = C = X \qquad (II)$$

wherein R and X have the above meanings, in toluene, xylene or some other aprotic solvent, at a temperature of 20 to 110 °C, the isocyanates of the general formula (II) wherein R represents a phenyl group, 1-naphthyl group or unsubstituted or substituted aromatic 5- member and 6-member rings having one or two hetero atoms being prepared *in situ* by means of Curtius rearrangement of the corresponding acid azide at elevated temperature.

Pharmaceutically acceptable acid addition salts, which also represent an object of the present invention, are obtained by reacting 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A with an at least equimolar amount of the corresponding inorganic or organic acid such as hydrochloric acid, hydroiodic acid, sulfuric acid, phosphoric acid, acetic acid, trifluoroacetic acid, propionic acid, benzoic acid, benzene

sulfonic acid, methane sulfonic acid, lauryl sulfonic acid, stearic acid, palmitic acid, succinic acid, ethylsuccinic acid, lactobionic acid, oxalic acid, salicylic acid and similar acids, in a solvent inert to the reaction. Addition salts are isolated by evaporating the solvent or, alternatively, by filtration after a spontaneous precipitation or a precipitation by the addition of a non-polar cosolvent.

9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A of the formula (I) and pharmaceutically acceptable addition salts with inorganic or organic acids thereof possess an antibacterial activity *in vitro*. Minimum inhibitory concentrations (MIC, mcg/ml) are determined by dilution method on microplates according to the recommendation of National Committee for Clinical Laboratory Standards (NCCLS, M7-A2). It is evident from Table 1 that standard strains and clinical isolates tested are susceptible to newly synthetised compounds. Thus they may be used for disinfection of rooms, chirurgical instruments and humans and as therapeutic agents in the treatment of infective diseases in animals, especially mammals and humans, caused by a broad spectrum of Gram-positive bacteria, mycoplasmas and generally patogenic microorganisms that are susceptible to the compounds of the formula (I). To this purpose the above compounds and pharmaceutically acceptable acid addition salts thereof may be administered orally in usual doses from 0.2 mg/kg body weight daily to about 250 mg/kg/day, most preferably from 5-50 mg/kg/day, or parenterally in the form of subcutaneous and intramuscular injections.

TABLE 1

Antibacterial *in vitro* activity of novel 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A in comparison with the starting amine

Test organism	MIC (mcg/ml)					
	9a-NH*	1	4	5	6	7**
Staphylococcus epidermidis ATCC 12228	3.12	6.25	25.0	3.12	6.25	6.25
Staphylococcus aureus ATCC 6538P	3.12	1.56	12.5	6.25	3.12	3.12
Micrococcus flavus ATCC 10240	1.56	3.12	12.5	6.25	3.12	1.56
Streptococcus faecalis ATCC 8043	3.12	3.12	6.25	3.12	3.12	1.56
Bacillus subtilis NCTC 8236	12.5	1.56	25.0	6.25	3.12	1.56
B.pumilus NCTC 8241	12.5	6.25	12.5	6.25	3.12	1.56
B.cererus ATCC 11778	3.12	6.25	12.5	12.5	6.25	6.25
Pseudomonas aeruginosa NCTC 10490	25.0	25.0	50.0	50.0	50.0	50.0
Esherichia coli ATCC 10536	3.12	12.5	12.5	12.5	25.0	12.5
Salmonella Panama 6117	3.12	6.25	25.0	25.0	>100.0	>100.0
BHS-A Streptococcus pyogenes J-21	3.12		12.5	3.12		
BHS-B Streptococcus Agalactiae J-22	1.56		12.5	1.56		

* 9-deoxo-9a-aza-9a-homoerythromycin A

** numbers designate newly synthetised compounds from the corresponding Examples

Process for the preparation of 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A of this invention is illustrated by the following Examples which should in no way be construed as a limitation of the scope thereof.

Example 1

9-deoxo-9a-N-(N'-isopropyl-carbamoyl)-9a-aza-9a-homoerythromycin A

A mixture of 9-deoxo-9a-aza-9a-homoerythromycin A (7.27 g; 0.01 mole), isopropylisocyanate (0.94 g; 0.011 mole) and toluene (40 ml) was stirred for 1 hour at the temperature of 30 °C. The reaction mixture was evaporated at reduced pressure (40 °C) to dryness to give crude 9-deoxo-9a-N-(N'-isopropyl-carbamoyl)-9a-aza-9a-homoerythromycin A (7.0 g; 86.2%), m.p. 128-136 °C. By recrystallization of the obtained product from a methanol-water mixture a chromatographically homogenous substance having the following physico-chemical constants was obtained:
m.p. 135~144 °C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.351.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.553.

IR (KBr) cm^{-1}	1730, 1625, 1515, 1455, 1380, 1270, 1165, 1050, 950.
^1H NMR (300 MHz, $CDCl_3$)δ	5.00 (1H, H-13), 4.85 (1H, H-1"), 4.47 (1H, H-1'), 4.02 (1H, H-3), 3.91 (1H, -CH$(CH_3)_2$), 3.50 (1H, H-5), 3.43 (1H, H-9a), 3.28 (3H, 3"-OCH_3), 2.49 (1H, H-9b), 2.32 [6H, 3'-$N(CH_3)_2$, 2.31 (1H, H-8), 1.62 (1H, H-7a), 1.29 (3H, 10-CH_3), 1.14 [6H,-CH$(CH_3)_2$], 1.13 (1H, H-7b), 1.04 (3H, 8-CH_3).
^{13}C NMR (75 MHz, $CDCl_3$)δ	175.5 (C-1), 158.2 (9a-NCONH), 103.8 (C-1'), 96.0 (C-1"), 87.9 (C-5), 78.8 (C-3), 48.8 (3"-OCH_3), 45.5 (C-2), 42.2 [-$CH(CH_3)_2$], 39.9 [3'-$N(CH_3)_2$], 27.4 (C-8), 22.9 [-$CH(CH_3)_2$, 20.5 (8-CH_3), 12.2 (10-CH_3).

Example 2

9-deoxo-9a-N-{N'-[(4-methyl-5-oxazole)-carbamoyl]}-9a-aza-9a-homoerythromycin A

A mixture of 9-deoxo-9a-aza-9a-homoerythromycin A (4.8 g; 0.0065 mole), 4-methyl-5-oxazole-carboxylic acid azide (1.0 g; 0.0066 mole) and dry toluene (30 ml) was heated for 15 minutes at the boiling temperature and then, by distillation at reduced pressure (40 °C), evaporated to dryness. The obtained residue was suspended in acetone (20 ml), stirred at room temperature and then the obtained crystals were filtered to give 9-deoxo-9a-N-{N'-[(4-methyl-5-oxazole)-carbamoyl]}-9a-aza-9a-homoerythromycin A (5.4 g; 93.3%), m.p. 174-177 °C. By recrystallization from hot acetone, a chromatographically homogenous product having the following physico-chemical constants was obtained:
m.p. 181~183°C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.149.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.491.

IR (KBr) cm^{-1}	1730, 1680, 1655, 1490, 1460, 1380, 1170, 1050, 755, 660.
^1H NMR (300 MHz, Py d_5, 50°C)δ	9.02 (9a-N-CONH), 7.95 (-CH=N) 5.71 (1H, H-13), 5.15 (1H, H-1"), 4.94 (1H, H-1'), 4.77 (1H, H-3), 4.07 (1H, H-5), 3.96 (1H, H-9a), 3.44 (3H, 3"-OCH_3), 2.50 (1H, H-9b), 2.32 [6H, 3'-$N(CH_3)_2$], 2.34 (1H, H-8), 2.35 (1H, H-7a), 1.68 (3H, 10-CH_3), 1.97 (1H, H-7b), 1.09 (3H, 8-CH_3).
^{13}C NMR (75 MHz, Py d_5, 50°C)δ	177.2 (C-1), 157.2 (9a-NCONH), 104.2 (C-1'), 96.9 (C-1"), 86.6 C-5), 80.5 (C-3), 50.1 (3"-OCH_3), 46.5 (C-2), 42.2 (C-4), 41.0 [3'-$N(CH_3)_2$], 29.1 (C-8), 21.2 (8-CH_3), 14.1 (10-CH_3), 149.9, 142.2, 128.2 and 12.2 (4-methyl-5-oxazole).

Example 3

9-deoxo-9a-N-[N'-(2-furyl)-carbamoyl]-9a-aza-9a-homoerythromycin A

Analogously to the process disclosed in Example 2, from 9-deoxo-9a-aza-9a-homoerythromycin A (2.18 g; 0.003 mole), 2-furancarboxylic acid azide (0.5 g, 0.0036 mole) and toluene (15 ml) a resinous residue (2.1 g) was obtained, wherefrom by chromatography on a silica gel column using the solvent system $CHCl_3$-CH_3OH (7:3) 9-deoxo-9a-N-[N'-(2-furyl)-carbamoyl]-9a-aza-9a-homoerythromycin A (1.7 g; 77.0%) having the following physico-chemical constants was obtained:

m.p. 155~159°C
TLC, EtAc-(n-C_6H_6)-tlHEt$_2$ (100:100:20), Rf 0.262.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.574.

IR ($CHCl_3$) cm^{-1}	1730, 1655, 1520, 1460, 1380, 1270, 1165, 1050, 1000, 955, 900, 830, 730.
^1H NMR (300 MHz, DMSO)δ	8.51 (9a-N-CONH), 7.24 (-O-CH=) 6.34 (-O-CH=CH-), 6.00 (-CH=C-NH), 5.04 (1H, H-13), 4.77 (1H, H-1"), 4.47 (1H, H-1'), 4.01 (1H, H-3), 3.42 (1H, H-5), 3.47 (1H, H-9a), 3.35 (3H, 3"-OCH_3), 3.25 (1H, H-9b), 2.50 [6H, 3'-$N(CH_3)_2$], 2.07 (1H, H-8), 1.45 (1H, H-7a), 1.20 (1H, H-7b), 1.15 (3H, 10-CH_3), 0.90 (3H, 8-CH_3).
^{13}C NMR (75 MHz, DMSO)δ	175.5 (C-1), 155.4 (9a-NCONH), 101.9 (C-1'), 95.3 (C-1"), 84.4 (C-5), 78.6 (C-3), 48.8 (3"-OCH_3), 44.6 (C-2), 40.0 (C-4), 40.1 [3'-$N(CH_3)_2$], 27.7 (C-8), 19.7 (8-CH_3), 13.2 (10-CH_3), 147.7, 136.5, 118.9, 98.0 (5-furanoyl).

Example 4

9-deoxo-9a-N-[N'-(4-pyridyl)-carbamoyl]-9a-aza-9a-homoerythromycin A

Analogously to the process disclosed in Example 2, from 9-deoxo-9a-aza-9a-homoerythromycin A (2.18 g; 0.003 mole), isonicotinic acid azide (0.53 g, 0.0036 mole) and toluene (15 ml) a resinous residue (2.26 g) was obtained, wherefrom by recrystallization from a methanol-water mixture 9-deoxo-9a-N-[N'-(4-pyridyl)carbamoyl]-9a-aza-9a-homoerythromycin A (1.9 g; 74.8%) having the following physico-chemical constants was obtained:
m.p. 149~1530°C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.089.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.441.

IR ($CHCl_3$) cm^{-1}	1730, 1650, 1590, 1510, 1460, 1380, 1330, 1280, 1165, 1050, 1000, 955, 900, 830, 730.
^1H NMR (300 MHz, DAMSO)δ	8.66 (9a-N-CONH), 8.25, 7.35 (4-piridyl), 5.16 (1H, H-13), 4.89 (1H, H-1"), 4.52 (1H, H-1'), 4.15 (1H, H-3), 3.53 (1H, H-5), 3.51 (1H, H-9a), 3.33 (3H, 3"-OCH_3), 3.28 (1H, H-9b), 2.34 [6H, 3'-$N(CH_3)_2$], 2.28 (1H, H-8), 1.62 (1H, H-7a), 1.23 (1H, H-7b), 1.36 (3H, 10-CH_3), 1.04 (3H, 8-CH_3).
^{13}C NMR (75 MHz, DMSO)δ	176.1 (C-1), 155.5 (9a-NCONH), 102.2 (C-1'), 95.5 (C-1"), 84.3 (C-5), 78.7 (C-3), 48.9 (3"-OCH_3), 44.8 (C-2), 40.2 (C-4), 40.4 [3'-$N(CH_3)_2$], 27.8 (C-8), 20.2 (8-CH_3), 14.4 (10-CH_3), 149.8, 148.0, 113.9 (4-pyridyl).

Example 5

9-deoxo-9a-N-(N'-phenyl-carbamoyl)-9a-aza-9a-homoerythromycin A

Analogously to the process disclosed in Example 2, from 9-deoxo-9a-aza-9a-homoerythromycin A (2.0 g; 0.0027 mole), benzoic acid azide (0.5 g, 0.0034 mole) and toluene (15 ml) a resinous residue (2.43 g) was obtained, wherefrom by chromatography on a silica gel column using a solvent system CH_2Cl_2-CH_3OH (85:15), 9-deoxo-9a-N-(N'-phenyl-carbamoyl)-9a-aza-9a-homoerythromycin A (1.4 g; 61.4%) having the following physico-chemical constants was obtained:
m.p. 126~130°C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.345.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.637.

IR (KBr) cm^{-1}	1730, 1645, 1600, 1539, 1510, 1455, 1380, 1315, 1240, 1165, 1045,950, 895, 755, 690.
^1H NMR (300 MHz, DMSO)δ	8.11 (9a-N-CONH), 7.30, 7.35 (phenyl), 5.05 (1H, H-13), 4.79 (1H, H-1"), 4.46 (1H, H-1'), 4.04 (1H, H-3), 3.46 (1H, H-5), 3.28 (1H, H-9a), 3.23 (3H, 3"-OCH_3), 3.16 (1H, H-9b), 2.34 [6H, 3'-$N(CH_3)_2$], 2.16 (1H, H-8), 1.58 (1H, H-7a), 1.15 (1H, H-7b), 1.25 (3H, 10-CH_3), 0.90 (3H, 8-CH_3).
^{13}C NMR (75 MHz, DMSO)δ	175.6 (C-1), 156.1 (9a-NCONH), 102.0 (C-1'), 95.4 (C-1"), 84.4 (C-5), 78.5 (C-3), 48.9 (3"-OCH_3), 44.6 (C-2), 39.4 (C-4), 40.1 [3'-$N(CH_3)_2$], 27.3 (C-8), 20.0 (8-CH_3), 14.0 (10-CH_3), 140.6, 127.9 and 114.4 (phenyl).

Example 6

9-deoxo-9a-N-(N'-benzyl-carbamoyl)-9a-aza-9a-homoerythromycin A

Analogously to the process disclosed in Example 1, from 9-deoxo-9a-aza-9a-homoerythromycin A (7.27 g; 0.01 mole), benzylisocyanate (1.33 g, 0.01 mole) and toluene (15 ml) a resinous residue (8.4 g) was obtained, wherefrom by chromatography on a silica gel column using a solvent system $CHCl_3$-CH_3OH (7:3), 9-deoxo-9a-N-(N'-benzyl-carbamoyl)-9a-aza-9a-homoerythromycin A (6.5 g, 75.6%) having the following physico-chemical constants was obtained:
m.p. 142~144 °C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.355.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.621.

IR (KBr)cm^{-1}	1730, 1630, 1525, 1410, 1380, 1270, 1165,1045, 950, 895, 755, 700.
^1H NMR (300 MHz, $CDCl_3$)δ	7.30, 5.00, 4.40 (-CH_2-C_6H_5), 5.04 (1H, H-13), 4.83 (1H, H-1"), 4.48 (1H, H-1'), 4.00 (1H, H-3), 3.52 (1H, H-5), 3.48 (1H, H-9a), 3.28 (3H, 3"-OCH_3), 2.51 (IH, H-9b), 2.56 [6H, 3'-$N(CH_3)_2$], 2.34 (1H, H-8), 1.66 (1H, H-7a), 1.10 (1H, H-7b), 0.99 (3H, 10-CH_3), 1.36 (3H, 8-CH_3).
^{13}C NMR (75 MHz, $CDCl_3$)δ	175.7 (C-1), 159.3 (9a-NCONH), 103.8 (C-1'), 96.5 (C-1"), 88.8 (C-5), 78.8 (C-3), 48.9 (3"-OCH_3), 45.9 (C-2), 40.4 (C-4), 40.2 [3'-$N(CH_3)_2$], 27.3 (C-8), 20.5 (8-CH_3), 12.3 (10-CH_3), 139.1, 128.3, 127.2 and 126.8, 45.9 (-CH_3-C_6H_5).

Example 7

9-deoxo-9a-N-(N'-benzyl-thiocarbamoyl)-9a-aza-9a-homoerythromycin A

Analogously to the process disclosed in Example 1, from 9-deoxo-9a-aza-9a-homoerythromycin A (7.27 g; 0.01 mole), benzylisothiocyanate (1.50 g, 0.01 mole) and toluene (30 ml) under stirring of the reaction mixture for 8 hours at the temperature of 30 °C, a resinous residue (8.6 g) was isolated, wherefrom by chromatography on a silica gel column using the solvent system $CHCl_3$-CH_3OH (7:3), 9-deoxo-9a-N-(N'-benzyl-thiocarbamoyl)-9a-aza-9a-homoerythromycin A (7.2 g; 82.1%) having the following physico-chemical constants was obtained:
m.p. 119~122°C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.370.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.689.

IR (KBr) cm^{-1}	1730, 1630, 1525, 1410, 1380, 1270, 1165, 1045, 950, 895, 755, 700.
^1H NMR (300 MHz, $CDCl_3$)δ	7.36, 4.85, 4.72 (-CH_2-C_6H_5), 4.75 (1H, H-13), 4.87 (1H, H-1"), 4.41 (1H, H-1'), 4.10 (1H, H-3), 3.81 (1H, H-11), 3.49 (1H, H-5), 3.30 (3H, 3"-OCH_3), 3.03 (1H, H-4"), 2.34 [6H, 3'-$N(CH_3)_2$], 2.31 (1H, H-8), 1.52 (1H, H-7a), 1.26 (1H, H-7b), 1.31 (3H, 10-CH_3), 0.96 (3H, 8-CH_3).

Example 8

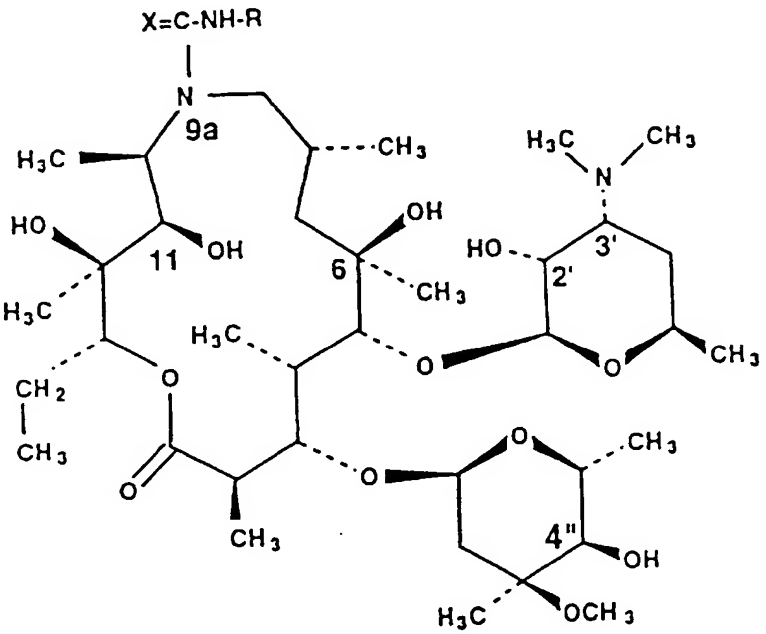
9-deoxo-9a-N-[N'-(1-naphthyl)-carbamoyl]-9a-aza-9a-homoerythromycin A

Analogously to the process disclosed in Example 1, from 9-deoxo-9a-aza-9a-homoerythromycin A (7.27 g; 0.01 mole), 1-naphthylisocyanate (1.7 g, 0.01 mole) and toluene (40 ml) by stirring the reaction mixture for 1 hour at the temperature of 20 °C a resinous residue (9.0 g) was isolated, wherefrom by chromatography on a silica gel column using the solvent system $CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1) 9-deoxo-9a-N-[N'-(1-naphthyl)-carbamoyl] A (7.8 g; 86.6%) having the following physico-chemical constants was obtained:
m.p. 134~137 °C
TLC, EtAc-(n-C_6H_6)-$NHEt_2$ (100:100:20), Rf 0.335.
$CHCl_3$-CH_3OH-conc. NH_4OH (6:1:0.1), Rf 0.658.

IR ($CHCl_3$) cm^{-1}	1740, 1635, 1530, 1500, 1455, 1380, 1340, 1265, 1160, 1050, 1010, 960, 890, 795, 775, 735; 700.

Claims

1. 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A of the formula (I)



wherein R represents a C_1-C_3 alkyl, aryl or aralkyl group and X represents O or S, and pharmaceutically acceptable addition salts thereof with inorganic or organic acids.

2. Substance according to claim 1, characterized in that R represents a C_1-C_3 alkyl group and X represents O.

3. Substance according to claim 2, characterized in that C_1-C_3 alkyl group represents an isopropyl group.

4. Substance according to claim 1, characterized in that R represents an aryl group and X represents O.

5. Substance according to claim 4, characterized in that the aryl group represents a phenyl group.

6. Substance according to claim 4, characterized in that the aryl group represents a 1-naphthyl group.

7. Substance according to claim 4, characterized in that the aryl group represents an unsubstituted or substituted 5-member or 6-member ring with one or two hetero atoms and X represents O.

8. Substance according to claim 7, characterized in that the heteroaryl group represents 4-methyl-5-oxazoyl group.

9. Substance according to claim 7, characterized in that the heteroaryl group represents furyl group.

10. Substance according to claim 7, characterized in that the heteroaryl group represents 4-pyridyl group.

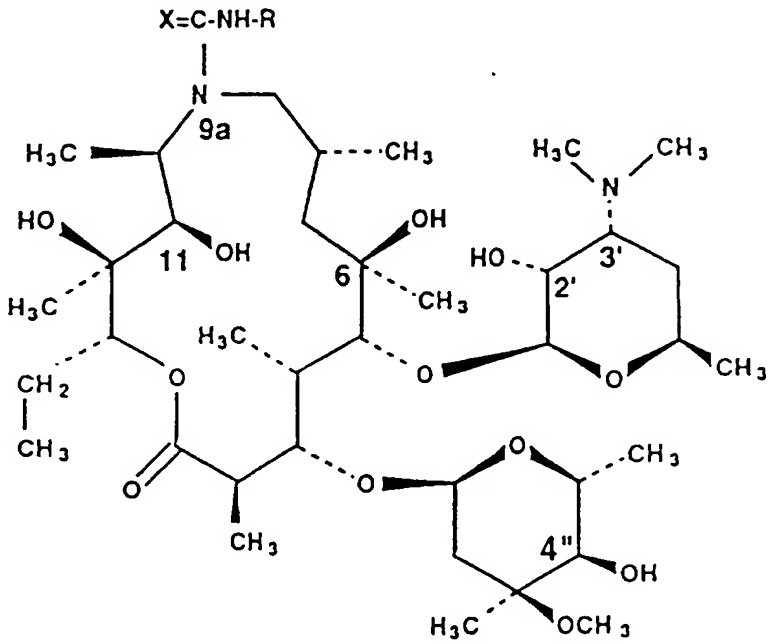
11. Substance according to claim 1, characterized in that R represents an aralkyl group and X represents O.

12. Substance according to claim 11, characterized in that R represents a benzyl group.

13. Substance according to claim 1, characterized in that R represents an aralkyl group and X represents S.

14. Substance according to claim 13, characterized in that R represents a benzyl group.

15. Process for the preparation of 9a-N-(N'-carbamoyl) and 9a-N-(N'-thiocarbamoyl) derivatives of 9-deoxo-9a-aza-9a-homoerythromycin A of the formula (I)



wherein R represents a C_1-C_3 alkyl, aryl or aralkyl group and X represents O or S, characterized in that 9-deoxo-9a-aza-9a-homoerythromycin A is reacted with isocyanates or isothiocyanates of the general formula (II)

$$R - N = C = X \qquad (II)$$

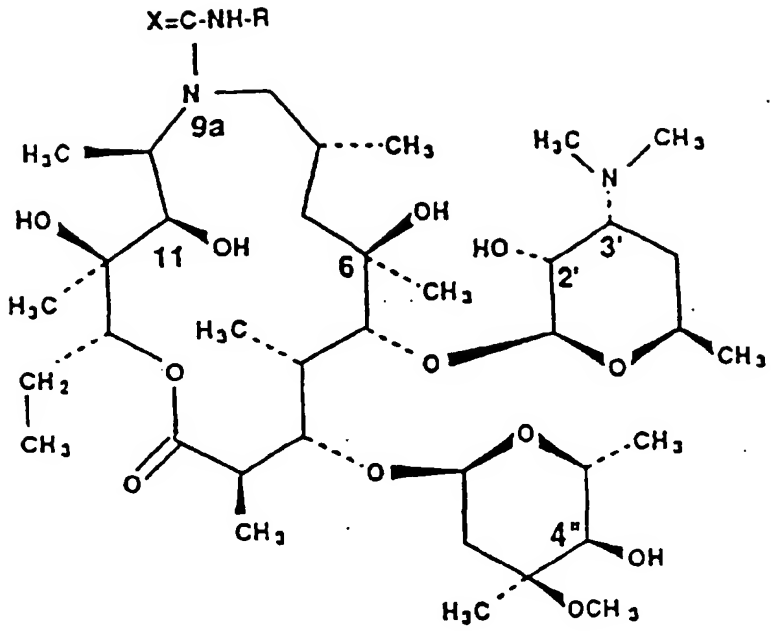
wherein R and X have the above meanings, in toluene, xylene or some other aprotic solvent, at a temperature of 20 to 110 °C, the compounds of the general formula (II) wherein R represents a phenyl group, 1-naphthyl group or unsubstituted or substituted aromatic 5- member and 6-member rings having one or two hetero atoms and X represents O or S being prepared *in situ* by means of Curtius rearrangement of the corresponding acid azide at elevated temperature.

16. Pharmaceutical composition comprising a pharmaceutically acceptable carrier and an antibacterially effective amount of the substances according to claim 1.

17. Use of a substance according to any of claims 1 to 14 for preparing pharmaceutical compositions for the treatment of bacterial infections.

Patentansprüche

1. 9a-N-(N'-Carbamoyl)- und 9a-N-(N'-Thiocarbamoyl)-Derivate von 9-Deoxo-9a-aza-9a-homoerythromycin A der Formel (I)



worin R eine C_1-C_3-Alkyl-, Aryl- oder Aralkylgruppe darstellt und X für O oder S steht, und ihre pharmazeutisch annehmbaren Additionsalze mit anorganischen und organischen Säuren.

2. Substanz nach Anspruch 1, dadurch gekennzeichnet, dass R eine C_1-C_3-Alkylgruppe darstellt und X für O steht.

3. Substanz nach Anspruch 2, dadurch gekennzeichnet, dass C_1-C_3-Alkylgruppe eine Isopropylgruppe darstellt.

4. Substanz nach Anspruch 1, dadurch gekennzeichnet, dass R eine Arylgruppe darstellt und X für O steht.

5. Substanz nach Anspruch 4, dadurch gekennzeichnet, dass die Arylgruppe eine Phenylgruppe darstellt.

6. Substanz nach Anspruch 4, dadurch gekennzeichnet, dass die Arylgruppe eine 1-Naphthylgruppe darstellt.

7. Substanz nach Anspruch 4, dadurch gekennzeichnet, dass die Arylgruppe einen unsubstituierten oder substituierten 5- oder 6-gliedrigen Ring mit einem oder zwei Heteroatomen darstellt und X für O steht.

8. Substanz nach Anspruch 7, dadurch gekennzeichnet, dass die Heteroarylgruppe eine 4-Methyl-5-oxazoylgruppe darstellt.

9. Substanz nach Anspruch 7, dadurch gekennzeichnet, dass die Heteroarylgruppe eine Furylgruppe darstellt.

10. Substanz nach Anspruch 7, dadurch gekennzeichnet, dass die Heteroarylgruppe eine 4-Pyridylgruppe darstellt.

11. Substanz nach Anspruch 1, dadurch gekennzeichnet, dass R eine Aralkylgruppe darstellt und X für O steht.

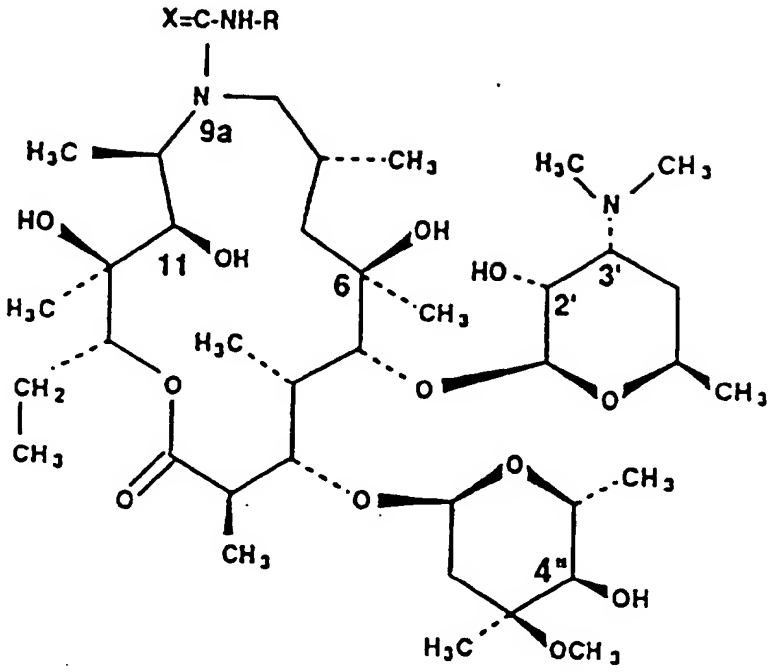
12. Substanz nach Anspruch 11, dadurch gekennzeichnet, dass R eine Benzylgruppe darstellt.

13. Substanz nach Anspruch 1, dadurch gekennzeichnet, dass R eine Aralkylgruppe darstellt und X für S steht.

14. Substanz nach Anspruch 13, dadurch gekennzeichnet, dass R eine Benzylgruppe darstellt.

15. Verfahren zur Herstellung von 9a-N-(N'-Carbamoyl)- und 9a-N-(N'-Thiocarbamoyl)-Derivaten von 9-Deoxo-9a-

aza-9a-homoerythromycin A der Formel (I)



worin R eine C_1-C_3-Alkyl-, Aryl- oder Aralkylgruppe darstellt und X für O oder S steht, dadurch gekennzeichnet, dass 9-Deoxo-9a-aza-9a-homoerythromycin A mit Isocyanaten oder Isothiocyanaten der allgemeinen Formel (II)

$$R\text{-}N = C = X \qquad (II)$$

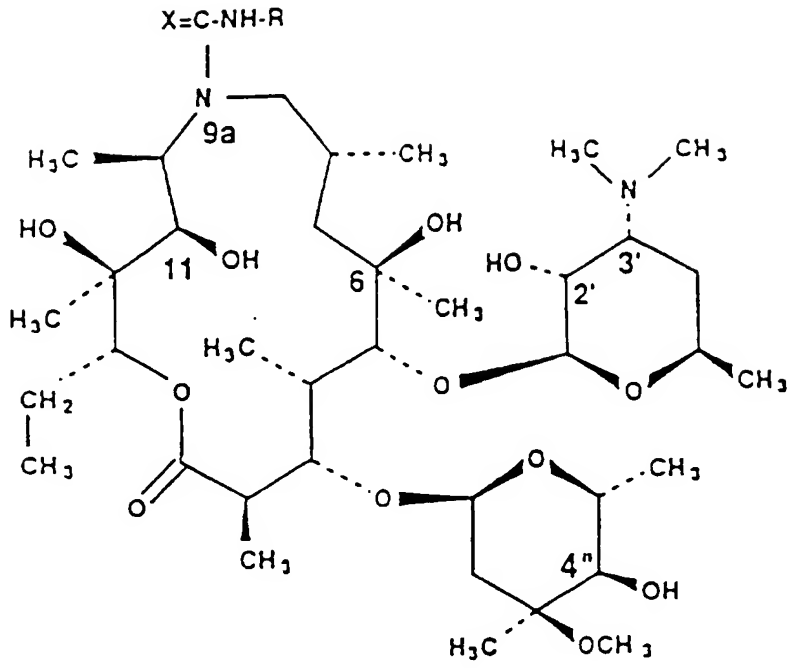
worin R und X die obengenannten Bedeutungen aufweisen, in Toluol, Xylol oder einem anderen aprotischen Lösungsmittel bei einer Temperatur von 20 bis 110°C umgesetzt wird, wobei die Verbindungen der allgemeinen Formel (II), worin R eine Phenylgruppe, eine 1-Naphthylgruppe oder unsubstituierte oder substituierte aromatische 5- und 6-gliedrige Ringe, die einen oder zwei Heteratome aufweisen, darstellt und X für O oder S steht, durch die Curtius-Umlagerung des entsprechenden Säureazids bei erhöhter Temperatur *in situ* hergestellt wird.

16. Pharmazeutische Zubereitung, dadurch gekennzeichnet, dass sie einen pharmazeutisch annehmbaren Träger und eine antibakteriell wirksame Menge von Substanzen nach Anspruch 1 enthält.

17. Verwendung der Substanz nach Ansprüche 1 bis 14 zur Herstellung von pharmazeutischen Zubereitungen zur Behandlung von bakteriellen Infektionen.

Revendications

1. Dérivés 9a-N-(N'-carbamoyl) et 9a-N-(N'-thiocarbamoyliques) de la 9-désoxo-9a-aza-9a-homoérythromycine A de la formule (I) :



dans laquelle R représente un groupe alkyle en C_1 à C_3, aryle ou aralkyle et X représente O ou S, ainsi que les sels d'addition pharmaceutiquement acceptables de ces composés avec des acides inorganiques ou organiques.

2. Composé suivant la revendication 1, caractérisé en ce que R représente un radical alkyle en C à C_3 et X représente O.

3. Composé suivant la revendication 2, caractérisé en ce que le radical alkyle en C_1 à C_3 est le radical isopropyle.

4. Composé suivant la revendication 1, caractérisé en ce que R représente un groupe aryle et X représente O.

5. Composé suivant la revendication 4, caractérisé en ce que le radical aryle est le groupe phényle.

6. Composé suivant la revendication 4, caractérisé en ce que le radical aryle est le groupe 1-naphtyle.

7. Composé suivant la revendication 4, caractérisé en ce que le radical aryle est un cycle pentagonal ou hexagonal, substitué ou non substitué, comportant un ou deux hétéroatomes et X représente O.

8. Composé suivant la revendication 7, caractérisé en ce que le radical hétéroaryle est le groupe 4-méthyl-5-oxazoyle.

9. Composé suivant la revendication 7, caractérisé en ce que le radical hétéroaryle est le groupe furyle.

10. Composé suivant la revendication 7, caractérisé en ce que le radical hétéroaryle est le groupe 4-pyridyle.

11. Composé suivant la revendication 1, caractérisé en ce que R représente un radical aralkyle et X représente O.

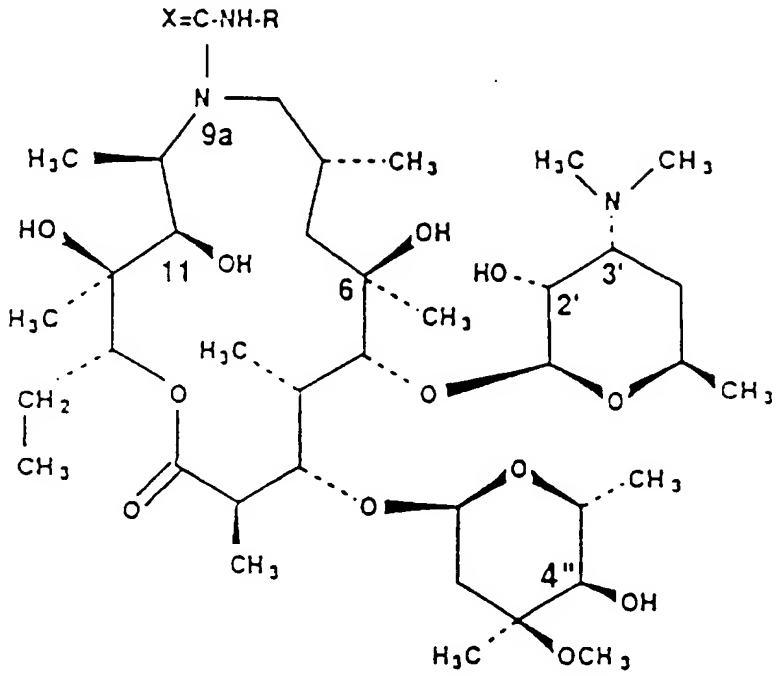
12. Composé suivant la revendication 11, caractérisé en ce que R représente le radical benzyle.

13. Composé suivant la revendication 1, caractérisé en ce que R représente un radical aralkyle et X représente S.

14. Composé suivant la revendication 13, caractérisé en ce que R représente le radical benzyle.

15. Procédé de préparation de dérivés 9a-N-(N'-carbamoyl) et 9a-N-(N'-thiocarbamoyliques) de la 9-désoxo-9a-aza-

9a-homoérythromycine A de la formule (I) :



dans laquelle R représente un groupe alkyle en C_1 à C_3, aryle ou aralkyle et X représente O ou S, caractérisé en ce que l'on fait réagir la 9-désoxo-9a-aza-9a-homoérythromycine A avec des isocyanates ou des isothiocyanates de la formule (II) :

$$R\text{-}N{=}C{=}X \qquad \text{(II)}$$

dans laquelle R et X possèdent les significations qui leur ont été précédemment attribuées, dans du toluène, du xylène ou tout autre solvant aprotique, à une température de 20 à 110°C, les composés de la formule générale (II), dans laquelle R représente le radical phényle, le radical 1-napthyle, ou des noyaux aromatiques pentagonaux et hexagonaux, non substitués ou substitués, possédant un ou deux hétéroatomes et X représente O ou S, étant préparés in situ par l'intermédiaire d'une transposition de Curtius de l'azide d'acide correspondant, à température élevée.

16. Composition pharmaceutique comprenant un véhicule ou excipient pharmaceutiquement acceptable et une quantité efficace du point de vue antibactérien des composés conformes à la revendication 1.

17. Utilisation d'un composé suivant l'une quelconque des revendications 1 à 14, en vue de la préparation de compositions pharmaceutiques convenant au traitement d'infections bactériennes.